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SOME OBSERVATIONS ON A NEW ORAL DIURETIC, MICTINE*

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IN THE CONTINUING SEARCH for a safe, effective non-mercurial oral diuretic, several agents have recently been evaluated in clinical trials.[1-11] Among these was Mictine, a brand of aminometramide, or 1-allyl-3-ethyl-6-aminotetrahydropyrimidinedione, chemically related to the xanthines.[5-11] The purpose of this study was to measure the diuretic response in hospitalized patients with congestive heart failure, and also to study the effects of long-term treatment in ambulatory patients with congestive failure.

MATERIALS AND METHODS

The clinical material is presented in Table I. Three patients were treated in hospital, and after discharge were followed up in the outpatient department. Observations were also made on 24 ambulatory patients with congestive heart failure who regularly attended the outpatient clinics of the Royal Victoria Hospital or who were followed up privately by one of us. Of these, 13 were women and 14 were men ranging in age from 44 to 79 years. Ten patients had hypertensive heart disease, ten others had arteriosclerotic coronary artery disease, six had rheumatic heart disease and one had cor pulmonale due to idiopathic pulmonary hypertension. One of the patients with arteriosclerotic heart disease had associated cirrhosis of the liver.

This group of patients had been treated for chronic congestive failure under our observation for periods ranging from three months to five years. At the onset of this study, the cardiac condition was fairly well compensated, and they were being treated with daily oral mercurial diuretics, or Diamox, moderate salt restriction (2-4 g. daily of NaCl), digitalis, ammonium chloride, and parenteral injections of Mercuhydrin (meralluride). The degree of failure was arbitrarily estimated on the frequency of mercurial injections required prior to the trial with Mictine. Thirteen were classified as having severe congestive failure, the criterion being requirement of one to two injections of a mercurial diuretic each week; six cases were considered as moderate in severity, the need for parenteral mercury being once in 2-3 weeks; the remaining eight were in mild failure and needed mercurial injection once a month or less often.

Visits to the clinic were made once or twice each week and the following data were recorded—weight, degree of œdema, and symptoms of congestion such as cough, dyspnœa or orthopnœa. Serum electrolyte studies were made in eight patients before and after trial therapy with Mictine, including determinations of sodium, potassium, chlorides, calcium and CO_2 combining power. Five patients were asked to measure their urine output, although no attempt was made to measure the intake or to keep it at a constant level. Urines were brought to the clinic periodically and the 24-hour sample was assayed for excretion of sodium, potassium and chloride, both during a control period and while the patient was taking the tablets.

Such studies were made for periods up to eight months. In three patients in hospital, similar assays were carried out on the wards, without the precaution necessary for accurate metabolic studies.

Mictine was added to the therapeutic regimen in 200-mg. tablets, one three times a day. The schedule was varied at times to study the effect of six tablets of Mictine per day, the effect on toxic symptoms of giving the drug before or with meals and the effect of the addition of oral ammonium chloride to the therapeutic response. Injections of a mercurial diuretic were added when the signs and symptoms of congestive failure could not be controlled by Mictine alone. The duration of therapy with Mictine ranged from three days to twelve months.

RESULTS

Nine patients could not tolerate Mictine because of anorexia, nausea and vomiting and so could not be included in the evaluation of diuretic response. The results are tabulated in Table I.

Each of the three hospitalized patients responded well to the addition of Mictine to their regimen, as judged by diuresis, loss of weight and improvement in clinical state. The diuresis in water was accompanied by increase in urinary sodium and chloride, but little change in the urinary excretion of potassium. The degree of diuresis was maintained for several days and then began to diminish along with a diminution in the excretion of urinary electrolytes.

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TABLE I.

Case No.	Age	Sex	Diagnosis	Degree of failure	Duration of failure	Duration of treatment	Frequency of mercurial injections		Toxic effects			Remarks
							Before Mictine	After Mictine	Nausea	Vomit	Anorexia	
1	49	F	H.C.V.D.	4+	3 years	8 mos.	1-2/wk.	0	0	0	0	
2	54	M	A.S.H.D.	2+	3 years	6 mos.	1-2/mo.	1-2/mo.	0	0	0	As good as other oral mercurial diuretic.
3	59	M	H.C.V.D.	4+	1½ years	5 mos.	1/wk.	0	0	0	0	
4	64	F	R.H.D.	2+	2 years	12 mos.	1-2/mo.	0	0	0	0	
5	59	F	H.C.V.D.	4+	5 years	3 days	1/wk.	1/wk.	+	+	+	Drug discontinued.
6	69	M	A.S.H.D.	1+	1 year	11 mos.	1/mo.	0	0	0	0	
7	59	M	H.C.V.D.	1+	2 years	3 wks.	1/mo.	1/mo.	+	+	+	Drug discontinued.
8	64	M	A.S.H.D.	1+	2 years	3 days	0-1/mo.	0-1/mo.	+	+	+	Drug discontinued.
9	62	M	A.S.H.D.	1+	1 year	2 wks.	1/mo.	1/mo.	+	+	+	Drug discontinued.
10	58	F	R.H.D.	4+	4 years	8 mos.	2/wk.	1/7-10 days	0	0	0	
11	62	M	H.C.V.D.	2+	6 mos.	7 mos.	0-1/mo.	0	+	0	0	
12	56	F	H.C.V.D. Cor. Thromb.	2+	18 mos.	6 mos.	1-2/mo.	0	0	0	0	
13	64	F	A.S.H.D.	2+	12 mos.	8 mos.	0-1/mo.	0	0	0	0	
14	80	F	A.S.H.D.	1+	2 years	4 mos.	0	0	0	0	0	
15	69	F	H.C.V.D.	3+	2 years	3 days	1/wk.	1/wk.	+	+	+	Drug discontinued.
16	69	M	A.S.H.D.	4+	2 years	12 mos.	1-2/wk.	1/wk.	0	0	0	
17	59	F	H.C.V.D.	2+	2 years	2 wks.	1-2/mo.	1-2/mo.	+	+	+	Drug discontinued.
18	44	M	Cor Pulmonale	4+	4 years	5 mos.	1-2/wk.	1/wk.	+	0	0	
19	65	M	H.C.V.D.	4+	3 years	8 mos.	1/wk.	0	0	0	0	
20	52	F	R.H.D.	4+	6 years	1 mo.	1-2/wk.	1-2/wk.	+	0	0	Poor response. Patient had ascites—card. cirrhosis.
21	52	M	A.S.H.D.	2+	1½ years	2 mos.	1-2/mo.	1/mo.	0	0	0	As good as oral mercurial diuretic.
22	53	F	R.H.D.	2+	4 years	4 mos.	1-2/mo.	1/mo.	0	0	0	As good as oral mercurial diuretic.
23	70	F	A.S.H.D.	1+	1 year	3 days	1/mo.	1/mo.	+	+	+	Drug discontinued.
24	65	M	A.S.H.D.	4+	5 years	2 weeks	1-2/wk.	1-2/wk.	+	+	+	Drug discontinued.
25	43	M	R.H.D.	3+	4 years	9 mos.	1/wk.	0-1/mo.	+	0	0	
26	62	F	H.C.V.D.	3+	4 years	6 mos.	1-2/wk.	1/7-10 days	0	0	0	
27	61	F	R.H.D.	3+	4 years	10 days	1/wk.	1/wk.	+	+	+	Drug discontinued.

A.S.H.D.—Arteriosclerotic heart disease.
H.C.V.D.—Hypertensive cardiovascular disease.
R.H.D.—Rheumatic heart disease.

There was no rebound phenomenon, however, and the urinary excretion of sodium did not fall below control levels. The increase in urine volume was concurrent with an improvement in the patients' condition and a decrease in body weight with loss of œdema fluid. Once the œdema was controlled, the continued administration of Mictine led to a maintenance of the dry state and the patients' well-being.

In two cases, an increase in dose of the drug from three to six tablets a day led to a slight increase in the diuresis. In two cases the addition of ammonium chloride usually led to transitory rise in the excretion of water and chloride but did not greatly influence the excretion of sodium and potassium.

In the ambulatory group of patients, of those classified as showing severe congestive failure, four patients could not tolerate the drug and it had to be discontinued within the first two weeks. Of the remaining nine cases, three were controlled by Mictine, digitoxin and a low salt diet without the use of other diuretics; in four others there was a slight reduction in the frequency of mercurial injections; in two cases there was little or no improvement with Mictine.

Of the 14 cases of moderate congestive failure, the drug had to be discontinued in five within the first two weeks due to severe gastro-intestinal complaints. Of the remaining nine cases, six were controlled with Mictine alone, and in three others the diuretic response was as good as with other oral diuretics (Neohydrin).

In four patients who had responded satisfactorily to the addition of Mictine to their regimen, withdrawal of the drug with continuation of digitalis and low salt diet soon led to a reaccumulation of œdema fluid with recurrence of symptoms of congestive failure. Continuous daily use of Mictine for long periods did not lead to tolerance and prevented fluctuations in retention of fluid as measured by body weight.

In five cases the addition of ammonium chloride to the regimen resulted in a slight increase in diuresis in three and had no effect in two.

SIDE-EFFECTS

As has been stated, nine of the original 27 patients studied in this report developed toxic symptoms from Mictine, severe enough to force withdrawal of the drug. All the symptoms were referable to the upper gastro-intestinal tract, with anorexia, nausea and vomiting as chief com-

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plaints. Toxic symptoms developed early in the course of treatment, usually within the first week and if they were not manifest by that time, did not come on with continued administration of the drug. An increase in the dose from three to six tablets per day increased the likelihood of the development of toxic symptoms.

ELECTROLYTE STUDIES

In eight patients, serum electrolytes were studied before, during and after the administration of Mictine. In no instance was there any significant change in the level of serum sodium, chloride, potassium or CO_2 combining power values. Serum non-protein nitrogen values were also estimated and showed no change other than could be expected from the disease state itself.

DISCUSSION

The above data confirm the earlier observations of others that Mictine has definite diuretic properties and can be used in the maintenance of patients with congestive heart failure. In many instances it can be used alone to control the œdema of such patients, and in others it may reduce the frequency of injections of mercurial diuretics required. Many of the patients had been treated with other oral diuretics (Diamox, Neohydrin) before the use of Mictine, and in many of the cases the response was as good or better with the latter.

In the three hospitalized cases, and in those clinic cases where 24-hour urine samples were collected, the diuresis was associated with an increase in sodium and chloride excretion in the urine, but the potassium excretion was only slightly increased or remained the same. Continued daily use of the diuretic over a long period of time did not lead to a state of tolerance. The diuresis persisted with the continued daily use of Mictine and decreased promptly when the drug was stopped.

The prolonged daily administration of Mictine did not produce any significant alteration in the serum sodium, chloride, potassium or CO_2 combining power of eight cases studied. In this study, the drug had to be discontinued in a third of the cases because of nausea and anorexia and occasional vomiting. This high incidence of gastro-intestinal complaints detracts greatly from the clinical usefulness of the agent. Our studies did not contribute to the fundamental mechanism of action of Mictine, but other observations indicate that the site of action is at the level of the renal tubule.[5-11]

SUMMARY

1. The diuretic effects of prolonged use of oral Mictine were studied in ambulatory patients with congestive heart failure for periods up to 12 months.

2. In one-third of the patients investigated, Mictine was useful in controlling cardiac œdema, but the high incidence of gastro-intestinal complaints may limit its clinical application.

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CONGENITAL CHYLOTHORAX

The development of the lymphatic system from six lymph spaces which in turn originate from the endothelium of adjacent veins is accepted. The occurrence of chylothorax in infants without an episode of trauma, mediastinal malignancy, tuberculosis or other mediastinitis may be termed congenital. Maintenance of nutrition in chylothorax is difficult because of the loss of fat and protein but intravenous infusion of the aspirated chyle is possible though hazardous. Since split fats are absorbed via the portal vein and unsplit fats via the chyle, the feeding of fatty acids gives more nourishment in these cases.

A trial of conservative treatment is warranted: frequent thoracentesis, a diet high in protein and split-fat products, parenteral plasma and water-miscible varieties of fat-soluble vitamins. Surgical intervention is indicated at the end of a three-week trial or if nutrition is not maintained. Since there are many communications of the thoracic duct with veins, ligation is proper treatment. It was first accomplished successfully in the neck by Cushing in 1898, and in the thorax by Lampson in 1946.

The chest should be entered on the side that is leaking, since there may be several fistulæ. Sites of leakage in the mediastinal pleura are sutured and a search is made for the thoracic duct for its multiple ligation. Injection of violet or green lipophilic dye two hours before operation may be of assistance.—J. G. Randolph and R. E. Gross, *A.M.A. Arch. Surg.*, 74: 405, 1957.